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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	29

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic[illegible]
09/126,945	Libermann et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Feb 7, 2001*.

2a) This action is **FINAL.** 2b) X This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *24-39, 43-100, 105-139, and 141-155* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) X Claim(s) *75-78, 80, 83-100, 121-124, and 126* is/are allowed.

6) X Claim(s) *24-39, 43-74, 79, 81, 82, 105-120, 125, 127-139, and 141-155* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)	Notice of References Cited (PTO-892)	18)	Interview Summary (PTO-413) Paper No.(s).
16)	Notice of Draftsperson's Patent Drawing Review (PTO-948)	19)	Notice of Informal Patent Application (PTO-152)
17) X	Information Disclosure Statement(s) (PTO-1449) Paper No(s). 24	20)	Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on 2/7/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/126,945 is acceptable and a CPA has been established. An action on the CPA follows.

The amendments filed 11/7/00 and 2/7/01 have been entered. Claims 40-42 and 140 have been cancelled. Claims 24, 43, 51, 67, 75, 76, 105-107, 109, 111, 113, 121, 122, 128, 129, and 137 have been amended, and new claims 149-155 have been added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Drawings & Specification

The formal drawings filed 2/22/01 are approved by the Draftsperson and the Examiner.

The disclosure is objected to because of the following informalities: The"Brief Description of the Drawings" (pages 2 and 3), specifically for Figures 1A-1C and 4-6, needs to be amended to reflect the new labeling present in the formal drawings filed 2/22/01, including where panels in the original figures are now given their own figure numbers.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 24-26, 28-29, 31-32, 34-35, 37-38, 43-53, 55-56, 58-59, 61-62, 64-65, 67-74, 79, 81-82, 105, 107, 109, 111, 113-120, 125, 127, 132, 134-135, 144, 146-147 and 149-155 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 24, 51, 105, 107 and 111 (and their dependent claims) recite the limitation that the nucleic acid encodes "a polypeptide which generates an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO: 2". Applicant has indicated that support may be found for this limitation at pages 24-25 of the specification, presumably the section entitled "Epitopes & Antibodies". However, this section of the specification clearly describes using PDEF itself, i.e. SEQ ID NO: 2, or antigenic fragments of PDEF to make antibodies against the protein of SEQ ID NO: 2. The specification does not teach using "variant" polypeptides, such as those encoded by the broadly claimed polynucleotides, in order to make antibodies against the protein of SEQ ID NO: 2. There is no evidence of record that one skilled in the art would even consider making a polypeptide differing in sequence from a known desired target protein or a fragment of the target protein in order to make antibodies against the target protein. Rather, as described in the specification one skilled in the art would use the target protein itself, or a fragment of it, in

order to make such antibodies. Consequently, this section of the specification does not describe, either implicitly or explicitly, the broad genus of polynucleotides now being claimed, i.e. polynucleotides that do not encode the recited fragments of the protein of SEQ ID NO: 2, yet could be used to generate antibodies that bind SEQ ID NO: 2. Contrast the rejected claims to claims 27 or 84, for example, which *are* directed to polynucleotides that encode the polypeptides described at pages 24-25 of the specification.

Claims 46, 48, 70, 72, 79, 81, 116, 118, 125, 127, 132, 134, 144, 146 (and claims dependent therefrom) each recite "said nucleic acid is operably associated with a *heterologous regulatory sequence*" (emphasis added). Claim 149 (and its dependent claims) recites "said nucleic acid is operably associated with *one or more regulatory elements* capable of directing *translation* of said amino acids" (emphasis added). It is unclear just what these terms are intended to convey. There is no clear support for these limitations in the original specification. The terms "heterologous regulatory sequence" and "regulatory elements" do not appear in the specification as originally filed, nor does any generic term equivalent to these terms. Page 27, line 27 to page 28, line 4 describes operable association of polynucleotides with specific elements, e.g. promoter, start and stop codons, that are required for either transcription and translation. Of these, only a promoter can be said to embrace a "regulatory sequence", and then only for transcription. The term "regulatory sequence" does not convey just what it is supposed to regulate or what the sequence is. The specification does not discuss regulating anything relative to the claimed subject matter, and especially does not discuss regulating translation. Page 18, line 23 to page 19, line 1

describes polypeptides, not polynucleotides. What the original specification does support is operable association of a "PDEF polynucleotide" with a promoter.

Claim 154 is directed to a method for making a polypeptide using a cell containing a recombinant polynucleotide of claim 149. The claim does not limit the identity of the polypeptide to that encoded by the recombinant polypeptide, nor even that the cell used be able to transcribe or translate the recombinant polynucleotide, for example if the cell were a mammalian cell and the "regulatory elements" were bacterial translation elements. Consequently, claim 154 reads on a method for producing any polypeptide that is made in the cell, not just the one encoded by the recombinant polypeptide. There is no support in the original specification for such a method. Claim 154 should be amended to provide some nexus between the "polypeptide" recited in claim 154 and the "60 contiguous amino acids" recited in claim 149.

Claims 137-139 and 141-148 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 137-148 are directed to polynucleotides comprising a nucleic acid, which encodes one of the recited epitopes of PDEF, fused "in frame" to a nucleotide sequence heterologous to SEQ ID NO: 1. Page 25, lines 10-16, which only discloses the epitopes, is alleged to provide support for this embodiment. Starting at line 28 of page 25, the specification discloses fusion

proteins comprising epitopes of PDEF as epitope tags. However, there is no apparent support for the generic embodiment instantly claimed with respect to "nucleotide sequence heterologous to SEQ ID NO: 1" in the context of a fusion to nucleic acid encoding an epitope of PDEF. There is no evidence of record that such a generic embodiment was contemplated by the inventors at the time the invention was made.

Applicant's arguments filed 2/7/01 have been fully considered but they are not persuasive. The amendment does not obviate the prior grounds of rejection since the claim still embraces a genus for which there is no description in the original specification, embracing embodiments where the "nucleotide sequence heterologous to SEQ ID NO: 1" does not encode a "second protein" (see specification page 25, lines 28-29). The phrase "fused in frame" has no meaning in the context of the claim as written because there is no indication of any element contained in the "nucleotide sequence heterologous to SEQ ID NO: 1" that has a "frame".

Claims 24-26, 28, 29, 31, 32, 34, 35, 37, 38, 40, 41, 43-53, 55, 56, 58, 59, 61, 62, 64, 65, 67-74, 105, 107, 109, 111, and 113-120 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 3/16/00 and below, because the specification, while being enabling for a "nucleic acid" that encodes SEQ ID NO: 2 or a fragment of SEQ ID NO: 2 (as recited in the claims), does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO: 2 or a recited fragment of SEQ ID NO: 2. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims have been amended to further limit the claimed polynucleotides to those which encode a "a polypeptide which generates an antibody that binds a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO: 2". Applicant has indicated that support may be found for this limitation at pages 24-25 of the specification, presumably the section entitled "Epitopes & Antibodies". However, this section of the specification clearly describes using PDEF itself, i.e. SEQ ID NO: 2, or antigenic fragments of PDEF to make antibodies against the protein of SEQ ID NO: 2. The specification does not teach using "variant" polypeptides, such as those encoded by the broadly claimed polynucleotides, in order to make antibodies against the protein of SEQ ID NO: 2. There is no evidence of record that one skilled in the art would even consider making a polypeptide differing in sequence from a known desired target protein or a fragment of the target protein in order to make antibodies against the target protein. Rather, as described in the specification one skilled in the art would use the target protein itself, or a fragment of it, in order to make such antibodies. This new limitation is not relevant to whether the polynucleotides are suitable hybridization probes or encode a functional PDEF protein, the claims still embrace many inoperative embodiments for these uses. With respect to making antibodies, while the claims are limited to operative embodiments by functional limitation, the specification does not enable one skilled in the art to make the polynucleotides without undue experimentation for the reasons of record and those set forth above.

Applicant's arguments filed 2/7/01 have been fully considered but they are not persuasive. Applicant states that undue experimentation is that which would "require a level of ingenuity beyond what is expected from one of ordinary skill in the filed" citing *Fields v. Conover*, 170 USPQ 276, 279 CCPA 1971). This statement has been taken out of context and is incomplete. The complete statement in *Fields v. Conover* is:

> As we recently remarked, a disclosure complies with the how-to-make requirement of 35 U.S.C. 112 even though "some experimentation, provided it is not an undue amount" (and provided that it does not require ingenuity beyond that to be expected of one of ordinary skill in the art), is still required to adapt the invention to particular settings. *In re Eltgroth*, 57 CCPA 833, 837, 419 F.2d 918, 921, 164 USPQ 221, 223 (1970).

Thus, applicants statement is a qualification of the admonition that a disclosure complies with the how-to-make requirement of 35 U.S.C. 112 even though "some experimentation, provided it is not an undue amount" may be required. The qualification being that the "some experimentation" permitted under the statute does not include experimentation that requires "ingenuity beyond that to be expected of one of ordinary skill in the art". In other words, if only a little experimentation is required but would require "ingenuity beyond ... skill in the art", the experimentation is undue. This case supports the rejection in that the amount of experimentation required to identify the operative embodiments is more than "some experimentation", it is an "undue amount" of making and testing: particularly when the specification does not direct one skilled in the art to using the broadly claimed polynucleotides to first make polypeptides that differ from SEQ ID NO: 2 and then use those variant polypeptides to make antibodies that bind SEQ ID NO: 2 . The situation here fails to meet the first test in *Fields v. Conover*.

Applicant then refers to *In re Wands*, 8 USPQ2d 1400, 1404 (CA FC 1988) which held that a considerable amount of experimentation is permitted if it is merely routine. The key in *Wands* was that the specification referred to well established prior art for making a particular kind of monoclonal antibody. Even though the making of monoclonal antibodies was a complex and laborious procedure, it was still one that one skilled in the art routinely performed with high expectation that the desired end result would be achieved.

The question here turns on whether the experimentation required to make the operative embodiments now claimed by functional language is "routine" under the law. Unlike the situation in *Wands*, the instant specification does not teach using a genus of polynucleotides that encode artificial polypeptide variants of PDEF (SEQ ID NO: 2) that are then used to make antibodies, not that bind the variant *per se*, but that bind PDEF. Furthermore, Applicant has provided no evidence that one skilled in the art would have even considered performing such a method for making antibodies to a known, characterized target protein, much less that those skilled in the art routinely practiced such a procedure at the time the instant application was filed. There is no nexus in the specification between the teachings for making variant polypeptides and making antibodies that bind to PDEF. These are two separate items. The specification teaches to make variant polynucleotides and polypeptides to optimize expression of PDEF or to improve biological function of PDEF or improve physical characteristics (see pages 15-17). For making antibodies that bind to PDEF, the specification (pages 24-25) teaches to use PDEF (SEQ ID NO: 2) or an antigenic fragment of PDEF; no mention is made of using variant polypeptides for this purpose.

Applicant argues (page 6) that the Examiner is incorrect in stating that routine experimentation under the law means that those in the art routinely engage in the type of experimentation required. The Examiner stands by this interpretation of the meaning of "routine" experimentation under the law. The Examiner agrees that the ultimate standard is whether "undue experimentation" would be required. However, if experimentation is required, one factor to be considered in order to determine whether such experimentation is undue is whether the experimentation is routine. Applicant then states that *In re Angstadt* and *Vaeck* (not citations provided) support the position that "the relevant factual issue is not whether Applicants have provided evidence that those skilled in the art routinely engage in the type of experimentation required, but rather, whether the experimentation needed to *test* whether a polynucleotide is encompassed by the claims is undue". It is unclear how *In re Angstadt*, 190 USPQ 214 (CCPA 1976) supports this position. The situation in *Angstadt* turned on several factors, one of which was that the specification had provided a list of catalyst compounds that had been found to be operative and provided detailed guidance for testing others. The Court also noted (page 218) that "each case must be determined in its own facts". The facts here are that the only predictably operative species disclosed are polypeptides consisting of SEQ ID NO: 2 and fragments thereof or fusion proteins comprising the fragments, e.g. fused to a carrier protein such as albumin, where the fragments would be unstable; and the specification provides no guidance or direction for using the claimed polynucleotides for the purpose that Applicant is advancing. It is also unclear how *In*

re Vaeck, 20 USPQ2d 1438 (CA FC 1991) applies either. There is no clear parallel in fact situation between *Vaeck* and the instant specification and claims.

Applicant argues that the specification teaches antigenic epitopes "found ... using DNAstar analysis", and that one skilled in the art would know not to alter these epitopes. The first statement is somewhat inaccurate. The specification discloses *putative* antigenic epitopes *predicted* by DNAstar analysis; their antigenicity was never confirmed. More to the point however, the rejected claims are not limited to polynucleotides that encode polypeptides wherein one or more of these epitopes are retained. This is the subject matter of allowed claims 84-100. Furthermore, whether the polypeptide retains at least one epitope is not the sole issue, but that the polypeptides embraced by the rejected claims would also contain new epitopes, unrelated to those of PDEF.

Claims 24-39, 43-74, and 105-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24, 51, 105, 107 and 111 (and their dependent claims) recite the limitation that the nucleic acid encodes "a polypeptide which *generates* an antibody that *binds* a polypeptide consisting of amino acids 1 to 335 of SEQ ID NO: 2" (emphasis added). First, it is unclear what the term "generates" means in this context. Polypeptides do not generate antibodies, although the immune systems of animals generate antibodies in response to a foreign protein or polypeptide.

Second, the meets and bounds of the claim are unclear with respect to what "binds" is intended to mean in this context. This limitation can be interpreted at least two different ways, that "bind" means a specific binding interaction between the antibody and an antigen, or that "bind" means a non-specific interaction between protein molecules.

Claim Rejections - 35 USC § 102

Claims 128-136 remain rejected under 35 U.S.C. 102(a) as being anticipated by GenBank Acc. No. AA662204 (Ref. AT-8 filed 2/11/99).

GenBank Acc. No. AA662204 discloses a isolated polynucleotide, plasmid vector (having heterologous promoters operably linked to the insert) and cell where the polynucleotide (514 nucleotides in length) comprises a nucleic acid, nucleotides 3-181, that is identical to nucleotides 1242-1420 of SEQ ID NO: 1 and that encodes 59 amino acids (amino acids 277-335) of SEQ ID NO: 2. Thus this nucleic acid is 99.4% identical to nucleotides 276-335 of SEQ ID NO: 1, which encodes 60 amino acids of SEQ ID NO: 2. The polynucleotide from positions 3-514 differs from nucleotides 1242-1753 of SEQ ID NO: 1 by only two nucleotides (at positions 1432 and 1440). The prior art polynucleotide includes codons for a DS dipeptide corresponding to SEQ ID NO: 2 positions 283-284, respectively, mentioned above, which anticipates the claims when m and n are either 237 and 238, respectively, or 241 and 242, respectively.

Claims 128-136 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (Dev. Biol. 151: 176-191, 1992).

Chen et al. disclose an isolated polynucleotide that encodes the *Drosophila* ets-4 polypeptide (page 182, Fig. 2C). Chen et al. discloses vectors comprising the polynucleotide, where a heterologous promoter is operably linked to the insert, and cells comprising the vectors (page 178 through page 179, col. 1). The ets-4 polypeptide has a DS dipeptide at residues 60-61, which anticipates the claims when m and n are either 237 and 238, respectively, or 241 and 242, respectively.

Double Patenting

Applicant remains advised that should claims 27, 30, 33, 36 and 39 be found allowable, claims 54, 57, 60, 63 and 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Applicant has indicated in the response filed 11/7/00 that cancellation of duplicate claims would be considered upon indication of allowability.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M. Hauda, can be reached on (703) 305-6608.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott D Priebe

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